Portfolio 2003: Toward a Cure for Parkinson's Disease

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Introduction

The National Institutes of Health (NIH) supports a wide range of scientific research aimed at discovering the cause(s) of Parkinson's disease (PD), with the ultimate goal of developing better treatments and preventing and/or curing the disease. As the second most common neurodegenerative disease, PD affects up to a million people in the US. In the last decade, the discovery of a variety of genetic mutations responsible for familial PD has opened up a wide range of new scientific research opportunities, from understanding the etiology and pathogenesis of the disease, to the identification of new potential therapeutic targets. In response to the conviction of the scientific community that there are extraordinary possibilities as well as in response to increasing public interest, the National Institute of Neurological Disorders and Stroke (NINDS) initiated PD research plans intended to accelerate the pace of research in PD and achieve the goal of reducing the burden of this disease through basic, translational and clinical research. The purpose of this editorial is to detail these planning efforts and progress towards achieving their goals.

The plans for PD

In January of 2000, in response to a congressional request, NINDS organized a large meeting of PD and other basic researchers from academia and industry, PD clinicians, ethicists, patient voluntary groups, and NIH staff. The resultant plan was the Parkinson's Disease Research Agenda, a 5-year research plan which articulates a broad set of scientific areas considered most important to pursue for the advancement of the PD research field (1). Since the creation of the Agenda, NINDS continues to initiate various programs to address the most timely Agenda recommendations as the science progresses (for archived solicitations, see (2). In addition, NINDS now "codes" the PD research portfolio of grants according to the scientific categories outlined in the Agenda, so that the amount and type of research going on in each area can be tracked.

In July 2002, NIH convened a scientific Summit to examine the current state of PD research in light of the Agenda at its midpoint (2.5 yrs), and to identify "roadblocks" that may still be impacting progress; for example, is there anything preventing progress on Agenda goals? Have scientific discoveries created new opportunities in PD since the creation of the Agenda? This exercise led to the development of the Parkinson's Disease Matrix, which complements the original Research Agenda, and identifies specific goals that can help eliminate roadblocks and further facilitate PD research (3). The matrix is a dynamic plan, one that is intended to evolve over time, as new findings continue to change the scientific landscape.

As planning efforts in PD are implemented, an annual analysis of the “world-wide” research effort in PD is crucial, not only to keep abreast of these new findings and assess progress on the Agenda and Matrix goals, but also for astute and judicious decision-making regarding future research initiatives, particularly since appropriation budgets for NIH are no longer doubling and are not known in advance. Moreover, measuring research progress against the goals outlined in these planning documents allows identification of additional research ‘gaps’ that warrant consideration by NIH leadership and staff, and ensure that the most timely scientific opportunities are addressed.

Identification and analysis of the FY03 Portfolio

The world-wide body of research includes federal research programs (NIH, Department of Defense (DOD), Department of Veterans Affairs (VA)), private efforts (foundations or other), and international research efforts. Parkinson’s planning originated at the NIH, given its substantial investment in PD research ($230 million in FY03), however, the portfolio analysis must necessarily include all ongoing substantial research endeavors so that an accurate representation is examined.

The NIH Parkinson’s disease portfolio is represented by a dozen different institutes whose missions include PD. Department of Defense grants include those funded in FY03 by the Neurotoxin Exposure Treatment Research Program (NETRP). This program is devoted to understanding exposures, such as psychological stress, toxic chemicals, chemical threat agents, head injury, and radio frequency radiation, which may predispose soldiers to neurodegenerative diseases (4); a central focus of the program is on Parkinson’s disease. The VA’s efforts in PD originate from the VA Healthcare System and Parkinson’s Disease Research, Education and Clinical Centers (PADRECCs). The network of PADRECCs is intended to provide a framework for VA researchers to collaborate and develop PD clinical expertise, scientific research and educational outreach (5). Private organizations, such as the Michael J. Fox Foundation (MJFF), fund a variety of research on Parkinson’s disease and many of these grants focus on very specific PD research needs, such as stem cells and biomarkers.

Lastly, Parkinson’s programs are ongoing in other countries around the world. While these activities cannot be measured within the same framework, they provide an additional window into the international scope of PD research. The available information was compiled for the NINDS Parkinson’s disease research website, along with country-specific PubMed searches, so it could be utilized as an additional reference tool in the PD portfolio analysis (6).

In order to measure the progress of PD research against the PD Research Agenda and Matrix, specific codes were created based upon the areas of interest as articulated in those planning documents. For a listing of each code and its definition, see Table 1. For FY03, over 1000 grants were reviewed and coded, generating a gestalt of how grants are distributed in terms of the science being pursued. Of the grants studied for the portfolio analysis, the general distribution of activities supported by different institutions, agencies, or foundations, is represented in Figure 1. NIH is responsible for approximately three quarters of the portfolio, with sizeable contributions by the DOD, VA and Foundation groups. The NIH portfolio can be further broken down into the various institutes, also shown in Figure 1. NINDS supports approximately 60% of the NIH total, followed by the National Institute on Aging (NIA), National Institute of Mental Health (NIMH) and the National Institute of Environmental Health Sciences (NIEHS). The twelve institutes formally invested in PD research, as well as the DOD and VA, comprise the Parkinson's Disease Coordinating Committee, which meets twice a year to allow for exchange of information on portfolios, and to ensure that there is not redundancy in effort across the NIH, or other agencies.

FY2003 Portfolio analysis and future needs

The portfolio can be analyzed in each of the four broad PD Agenda categories; following is a synopsis of ongoing research in each area, along with identified gaps and suggestions on how they may be addressed.

I. "Understanding Parkinson's disease"

Understanding the etiology of Parkinson's disease involves the study of genetic and environmental causes, as well as mechanisms of cell death and subsequent changes in neuronal circuitry. Large portions of the federal, private, and international portfolio are invested in this area (Fig 2a), and the field has expanded over the past several years. Since the landmark discovery in 1997 of genetic mutations that cause or contribute to PD, the tremendous wealth of tools available in genetic, molecular and cellular biology can now be applied to PD. Recent discoveries of mutations in DJ1, Pink1, and triplication mutations in alpha synuclein (7, 8, 9) have expanded the potential variety of molecular pathways that contribute to the degeneration and death of neurons. Understanding how these mutations affect normal cellular functions and cause malfunctioning of a cell's protein processing machinery will be essential to targeting points for therapeutic intervention. It is now widely recognized that these cellular degeneration mechanisms may be common to a variety of neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, etc. These studies for PD may well benefit other neurodegenerative disease research, and conversely, work on these other diseases is likely to help PD research. While these basic science studies continue, additional resources could aid their progress. The combination of data sets from existing genetic and epidemiological cohorts could help accelerate progress in both gene discovery and in the understanding of combined genetic/environmental causes of PD. Additionally helpful to the former would be an annotated genetic database of all relevant mutations discovered in PD. Better animal models that recapitulate gene-environment interactions in the etiology of the disease would benefit the latter, as would standardized experimental guidelines for the use of toxicants in PD models. Finally, it is clear that understanding the circuitry changes associated with disabling dyskinesias will be crucial to developing better interventions for those symptoms.

II. "Developing New Treatments for Parkinson's disease"

Current treatments for Parkinson's disease involve two approaches: pharmacological therapies and surgical interventions (see Fig. 2b). Recently, the exploration of pharmacological interventions for PD has been invigorated by the launch of the Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD), a series of pilot trials of potential neuroprotectants, which will be followed by a large, simple efficacy trial if agents are found to warrant further investigation. All neuroprotectants were selected through a critical evaluation process that represents a novel approach in intervention strategy (10). While promising drugs continue to be evaluated, challenges remain. As the search for new drugs continues, and high throughput screening efforts identify new compounds, additional testing in animal models will be needed before initiating new pilot studies. Moreover, while neuroprotection strategies are aimed at slowing or stopping disease early in its course, better treatments for those with advancing disease are still needed, particularly for those with dyskinesias and non-motor symptoms such as depression or dementia. Prior to the creation of the Agenda there had been no trials of depression in PD; a funded trial is now ongoing, as is a study of dementia in PD in the NINDS intramural program.

The primary surgical intervention for PD is Deep Brain Stimulation (DBS). The Federal portfolio has a large investment in this area, including research on the circuitry and physiology of DBS, better technology for DBS, and large-scale clinical trials done in collaboration between NINDS and the VA. Improved outcome measures overall are needed to ensure adequate evaluation of all clinical interventions. Patient participation is the key element to the ultimate success of all clinical trials, and continued efforts in patient education, recruitment, and involvement in Institutional Review Boards (IRBs) will be required.

Current pharmacotherapy and surgical interventions primarily treat the symptoms of PD. NET-PD is devoted to finding drugs which may address the underlying disease. Developing *new* treatments or approaches which can address the underlying disease remains challenging. Efforts to develop stem cells and gene therapy as rational therapeutic treatments for PD are ongoing as shown in Figure 2b. Important milestones for the development of gene therapy are being met, such as the creation of regulated vectors (11), as are achievements for stem cell therapies (12, 13). However, additional studies could be pursued which could expand this field even further into the realm of new therapeutics. Studies of intrinsic repair mechanisms are needed, such as explorations of endogenous triggers for elevated growth factor expression, such as glial derived neurotrophic factor (GDNF), or differentiation of endogenous stem cells to replace dying dopaminergic neurons. Studies of small interfering RNAs (RNAi) are just beginning (14), but show great promise for neurodegenerative diseases (15), and should be expanded to PD. Exploration of neurotrophin analogues, RNAi, or other small molecules engineered to PD therapeutic targets that can bypass the blood-brain barrier will be required. Investigations such as these will be crucial for taking advantage of the promise of neurotrophic factors, stem cells, and RNAi in a non-invasive manner.

"Creating New Research Capabilities"

New research capabilities include the infrastructure and resources needed to facilitate Parkinson's research on all levels. These include repositories for DNA, brain tissue, and PD animal models, as well as microarray resources and drug libraries. Many resources are becoming available (Fig. 2c), including the DNA Repository at Coriell (16), and the PD mouse modeling facility at UCLA (17). Sharing of genetic samples and transgenic or knock out animal models should be encouraged to allow these new resources to expand. Standardization and centralization could maximize the value of all resources, while education regarding procedures for access would maximize their use. For example, existing brain banks could be networked, and patient awareness of the importance of brain donation should be emphasized. NINDS has recently requested applications for the creation of a PD Data Organizing Center (18). The PD-DOC will centralize and coordinate these resources, as well as collect patient clinical data from PD centers throughout the country, for use by the PD research community.

A currently unavailable resource in PD is biomarkers. The discovery of biomarkers which could allow for early diagnosis or facilitate the assessment of clinical interventions in the disease is crucial; Biomarkers that could assist in assessing the diagnosis or prognosis of PD would be an invaluable tool. Additional emphasis should be placed on this particular area, because advancement of many other goals for PD research depends on a reliable biomarker by any of its formal definitions (19).

"Enhancing the Research Process"

Enhancing the research process includes creative funding strategies or other approaches that can assist in removing roadblocks to PD research. Training grants, special meetings and workshops, and ethics are all included in these activities, and efforts on these fronts should continue. Public-private partnerships provide creative approaches to increased and more rapid funding for Parkinson's research. In these areas, the foundation groups excel (fig. 2d) due to their ability to rapidly fund research projects in targeted areas. In addition, private foundation groups such as the MJFF can fund research that federal agencies cannot, for example, work on stem cell lines which are not within the federal register. Training fellowship programs and start up grants, such as those funded by the American Parkinson's Disease Foundation (APDA), the Parkinson's Disease Foundation (PDF), and the National Parkinson's Foundation (NPF), are invaluable to helping new investigators begin new careers devoted to PD, as well as fund start-up projects which may not be ready for larger grant submissions to the NIH. Groups such as the Parkinson Alliance encourage specific research on DBS and partner with the NIH in the DBS consortium and its related activities. These PD foundation groups, led by the PDF, are mounting a large scale effort to develop an international congress for PD research at all levels, which will provide a single forum through which the science can be disseminated and communicated. Ethical issues are also emerging in PD research, with the advent of commercially available genetic testing (see 20). As science continues to advance, it will be vital for patients to understand the ethical consequences and impact on their lives.

Summary

Questions are frequently posed as to the wisdom of disease specific planning efforts in the biological sciences (21). Because it is not always known where a fundamental discovery may be made that could profoundly advance a particular scientific field, NIH has maintained a commitment to investigator initiated endeavors which form the solid foundation of biological understanding. However, it is also evident that when there is a commitment to excellence in disease-specific research, both expected and unexpected findings contribute importantly to many biomedical research fields, as evidenced by decades of cancer research, and more recently, AIDS research. In addition, disease-specific research is needed in order to translate basic discoveries into novel and usable therapeutics for diseases.

Over the past several years, much progress has been made towards advancing PD research through basic neuroscience research, as well as through the planning efforts described above. There is an important balance which must be achieved that allows for the following: serendipitous discoveries across basic neurosciences, focused basic PD research, goal directed translational neuroscience which will develop new therapeutics, and successful selection of the most promising clinical trials. NIH has several tools which can be used to strike the most appropriate balance. *Tracking the science*, as done for the PD portfolio, will allow for the identification of gaps in understanding of PD, as well as to ensure that redundant efforts are not being made across institutes or agencies. NIH is also well equipped to *build infrastructure where needed*; frequently this infrastructure assists not only in providing the community with much-needed resources in a standardized manner, but also in rapidly capitalizing on unexpected scientific discoveries. Finally, goals can be directed towards *clear scientific opportunities* based on these kinds of findings, or towards areas which would benefit more than one disease area, expanding the resultant ‘payoff’ from the relative investment. Through careful utilization of these tools, adherence to the PD research Agenda and Matrix as they evolve, with the underpinnings of basic neuroscience, it is hoped that the cure or prevention of PD will be closer than ever.

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Table 1. Definitions of scientific coding categories.

Scientific Codes	**Definition**	**Related codes**
Understanding Parkinson's		
Genetics	Gene discovery, regulation, expression, in PD.	Repositories
Environmental Studies And Epidemiology	Gene environment interactions, toxic exposures, risk factors.	'Death' of neurons
"Life and Death" of Neurons	"Life": general cell biology of DAergic or other neurons, protein function. "Death": oxidative stress, mitochondrial impairment, protein aggregation, cell death pathways (apoptosis, toxic exposures, etc.).	
Circuits	Mechanism, organization, and patterns of neuronal activity in normal and PD models.	DBS
Developing New Treatments		
Pharmacological Approaches	Basic studies of pharmacological or pharmaceutical treatments, also all clinical studies and trials of pharmacological interventions.	
Deep Brain Stimulation (DBS)	Basic studies and animal modeling of DBS, technology improvement, DBS trials.	Circuits
Outcomes/Evidence Based Medicine	Outcome measures, methologies, global statistics	
Cell Implantation	Differentiation, development, characteristics of stem cells for PD; cell implantation in PD animal models.	
Gene Therapy	Development of CNS viral vectors (promoters, regulated elements, etc); Gene transfer science, including efficacy and side effects in PD animal models (inflammation, toxicity, duration of expression, insertional recombination, etc)	
Rehabilitation	Rehabilitation of movement, posture, coordination, or non-motor symptoms; includes exercise and homeopathic therapies.	
Non-Motor Studies	Depression, dementia, all autonomic complications, speech impairment, micrographia.	
Translational Research	Therapy development necessary prior to clinical testing (preparation of data required for Investigational New Drug application)	
Creating New Research Capabilities		
Microarrays	Microarray resources, or their use in PD studies	
Biomarkers	Imaging or other biomarkers	Neuroimaging
Brain Banks/Repositories	Resource repositories, or development of resource standards/guidelines.	Genetics
High Throughput Screening	Assay development, screening for compounds in PD models	Translational Research
Models of PD	Development of genetic or other animal models, use of models in PD research	
Neuroimaging	Development of imaging technology or ligands, use of imaging in research.	Biomarkers
Enhancing the Research Process		
Ethics	Ethics at any level of the research process	
Innovative Funding Mechanisms	Supplements, fast tracked initiatives, special funding mechanisms	Public-private partnerships
Public-Private Partnerships	Partnering with groups outside NIH	Innovative funding
Other Accomplishments	Workshops, meetings, special training or fellowships.	

Fig. 1. Distribution of FY03 PD Research Activities

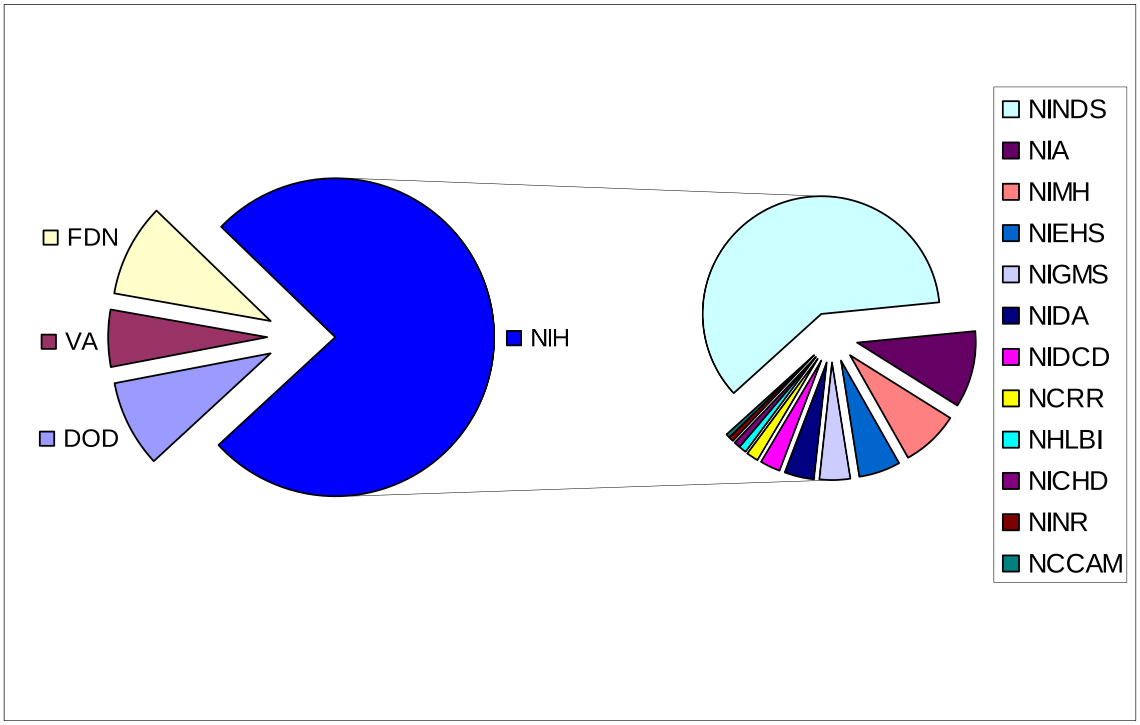
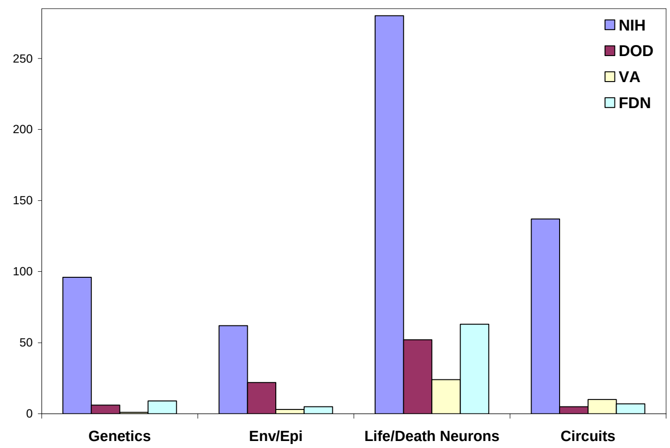


Figure 1. Distribution of FY03 PD Research Activities.

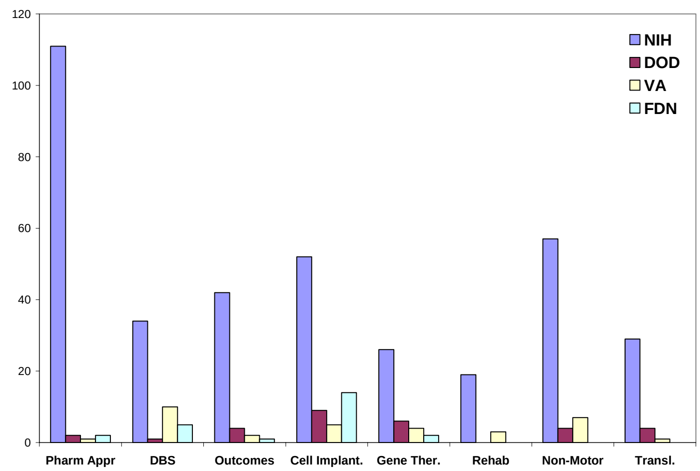
The pie chart on the left depicts the number of research activities (grants or other awards) broken down by category: National Institutes of Health (NIH), Department of Defense (DOD), Veterans Administration (VA), and private foundation groups (FDN). The NIH portion is further divided into individual institutes which fund Parkinson's research.

Figure 2. Distribution of Activities across Agenda Categories.

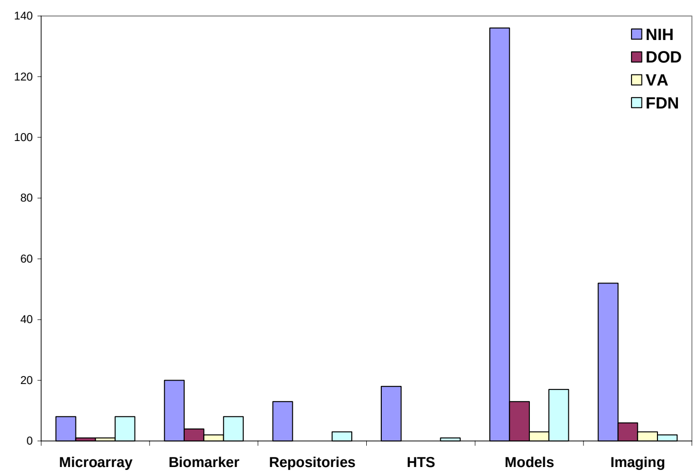
a. Understanding Parkinson's Disease



b. Developing New Treatments



c. Creating New Research Capabilities



d. Enhancing the Research Process

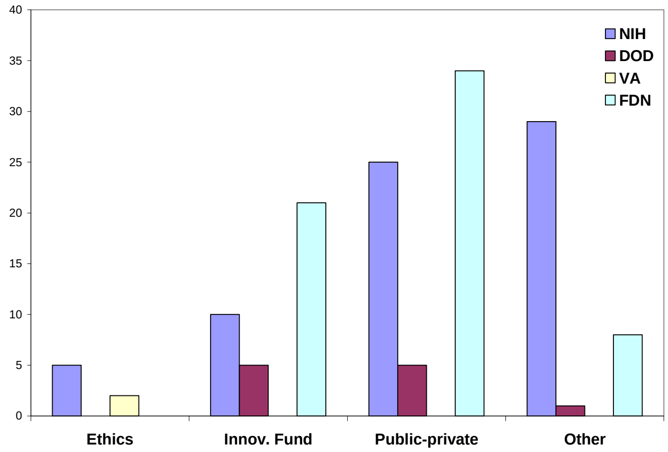


Figure 2. Distribution of Activities across Agenda Categories

A through D shows a schematic breakdown of the number of research activities sponsored by each primary funding group (NIH, DOD, VA, and FDN) in each of the 4 broad areas of the Parkinson's Research Agenda. These broad areas are subdivided into the research topics of interest as defined in Table 1.